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09/879,959	09/12/2001	Paul H. Weigel	3554.049	6465

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EXAMINER	
WAX, ROBERT A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/879,959	WEIGEL ET AL.	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-14,39-41 and 60-312* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14,39-41 and 60-312* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11142003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement filed November 13, 2003 has been considered. Please see the attached initialed PTO-1449. References 1, 6, 12, 14 and 18-27 were lined through because they did not discuss hyaluronic acid and seemed to have been cited by mistake. References K-O were lined through because Examiner does not read Japanese.

Drawings

2. The drawing of Figure 14 was received on September 12, 2001. This drawing is acceptable.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 11, 39-41, 60-63, 67-81, 90-98, 117-119, 126-133, 150-163, 192-224, 247-257 and 280-290 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant methods of producing hyaluronic

acid wherein the DNA encoding the hyaluronate synthase is from Streptococcus equisimilis or Streptococcus pyogenes, does not reasonably provide enablement for recombinant methods of producing hyaluronic acid wherein the DNA encoding the hyaluronate synthase is from other sources, including Group A HAS and Group C HAS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant claims read on Bacillus host cells comprising DNA encoding enzymatically active hyaluronan synthase, recombinant methods of producing hyaluronic acid and hyaluronic acid produced by those processes wherein the DNA encoding the hyaluronate synthase is from any organism whatsoever, or Group A organisms or Group C organisms. These latter are informal names given to groups of organisms that produce Group A or Group C hyaluronan synthase, respectively. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to Bacillus host cells comprising DNA encoding enzymatically active hyaluronan synthase, recombinant methods of producing hyaluronic acid and hyaluronic acid produced by those processes wherein the DNA encoding the hyaluronate synthase is from any organism whatsoever, or Group A organisms or Group C organisms.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, (1) the amount of experimentation is very large because of the large number of organisms that produce hyaluronic acid (almost all organisms on the planet); (2) the amount of guidance provided by the specification is limited since only the isolation of the gene from *S. equisimilis* is shown. More guidance is needed in view of the evidence in the specification that the DNA encoding seHAS and that encoding spHAS do not cross-hybridize. This shows that one of skill in the art would not expect to be able to use the disclosed DNA as a probe to isolate DNA encoding

other hyaluronate synthases from other organisms. Additionally, there is no guidance as to what might constitute an organism that makes Group A or Group C hyaluronan synthase. Continuing, (3) the specification shows how the DNA encoding seHAS was obtained; (4) the nature of the invention is the placement of DNA encoding hyaluronate synthase into a host cell to force manufacture of hyaluronic acid. The prior art (5) shows that hyaluronic acid is well known, that membranes comprising hyaluronate synthase have been used to prepare hyaluronic acid and that Applicants are apparently the first to isolate the DNA encoding seHAS; (6) the relative level of skill in this art is very high; (7) the predictability of the art is low since, with no useful probe, finding a needle in a haystack would be much easier than finding the DNA encoding the desired enzyme. Finally, (8) the claims are enormously broad because any DNA encoding any hyaluronate synthase is encompassed by the claims.

Based on this analysis, the conclusion that it would require undue experimentation to practice the instant invention is inescapable.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

5. Claims 11, 39-41, 60-63, 67-81, 90-98, 117-119, 126-133, 150-163, 192-224, 247-257 and 280-290 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are

directed to Bacillus host cells comprising DNA encoding enzymatically active hyaluronan synthase, recombinant methods of producing hyaluronic acid and hyaluronic acid produced by those processes wherein the DNA encoding the hyaluronate synthase is from any organism whatsoever, or Group A organisms or Group C organisms and is defined only by one functional characteristic (i.e., the DNA encodes hyaluronate synthase). The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

Just as the claims at issue in *UC v. Lilly* defined the invention by the function of the claimed DNA (encoding insulin), the instant claims define the DNA used in the claimed process only by one of its functional properties. The court held this sort of functional definition insufficient. "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes

that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." *UC v. Lilly*, at *24-*25, thus, the above claims lack adequate written description.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 150-191 and 280-312 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Meyer et al.

Meyer et al. teach hyaluronic acid. This teaching clearly anticipates the above claims. Applicant has made no showing as to what the differences might be between the claimed hyaluronic acid and that taught by Meyer et al.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 11, 39-41, 60-63, 67-77, 192-213 and 236-246 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,455,304. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed method of making hyaluronic acid is a variation of the invention of the patented claims to *S. pyogenes* nucleic acid, vector and *Bacillus subtilis* host cells; such claims would not have been restricted, had they appeared in the same application.

10. Claims 11-14, 39-41, 62-66, 69-149 and 192-279 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 60-67 and 69-73 of copending allowed Application No. 09/469,200. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the instantly claimed method of making hyaluronic acid is a variation of the invention of the allowed claims to *S. equisimilis* nucleic acid, vector and host cells; such claims would not have been restricted, had they appeared in the same application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 11, 39-41, 60-63, 67-77, 192-213 and 236-246 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 43-61 of copending Application No. 10/117,795. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed method of making hyaluronic acid is more general than the method of making hyaluronic acid in the other application, which is limited to nucleic acid from *S. pyogenes*.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 11, 39-41, 60-63, 67-77, 192-213 and 236-246 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 60-64 of copending Application No. 10/011,771. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed method of making hyaluronic acid is a

variation of the invention of the other claims to nucleic acid encoding at least *S. pyogenes* hyaluronate synthase; such claims would not have been restricted, had they appeared in the same application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 11-14, 39-41 and 60-312 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 60-72 of copending Application No. 10/011,768. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed method of making hyaluronic acid is a variation of the invention of the other application's claims to nucleic acid, vector and *Bacillus subtilis* host cells; such claims would not have been restricted, had they appeared in the same application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 11, 39-41, 60-63, 67-77, 192-213 and 236-246 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 and 35-42 of copending Application No. 10/124,222. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed method of making hyaluronic acid is a variation of the invention of the other application's claims to *S. pyogenes* nucleic acid,

and method of making hyaluronic acid; such claims would not have been restricted, had they appeared in the same application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 11, 39-41, 60-63, 67-77, 192-213 and 236-246 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-309 of copending Application No. 10/172,527. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed method of making hyaluronic acid is a variation of the invention of the other application's claims to nucleic acid, vector and *Bacillus subtilis* host cells; such claims would not have been restricted, had they appeared in the same application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

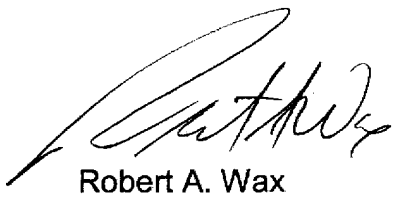
16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-

0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert A. Wax
Primary Examiner
Art Unit 1653

Notice of References Cited	Application/Control No. 09/879,959	Applicant(s)/Patent Under Reexamination WEIGEL ET AL.	
	Examiner Robert A. Wax	Art Unit 1653	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Meyer et al., "The Polysaccharide of the Vitreous Humor," J. Biol. Chem., vol. 107, pp. 629-634, 1934.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

THE POLYSACCHARIDE OF THE VITREOUS HUMOR

By KARL MEYER and JOHN W. PALMER

(From the Biochemical Laboratory of the Department of Ophthalmology of the College of Physicians and Surgeons, Columbia University, New York)

(Received for publication, September 4, 1934)

Since the work of Mörner (1) the existence of a mucoid in the vitreous humor has seemed well established. All subsequent workers used his method of preparation: the precipitation of the diluted native vitreous humor with dilute acetic acid. In his recent book on the nature of the vitreous body (2), Duke-Elder gives its concentration as 0.021 per cent, or about 30 per cent of the total protein present. The only analysis we were able to find on this mucoid is that of Mörner: N, 12.27 per cent; S, 1.19 per cent.

The stability of a typical mucoid, as, for example, egg mucoid, toward splitting into its polysaccharide and protein components is very remarkable. Thus Levene and Mori (3) state that the egg white must be hydrolyzed on the steam bath with 10 times its volume of 10 per cent barium hydroxide for 7 hours.

In an effort to prepare the supposed vitreous mucoid for other studies, we obtained, by very gentle methods, a free polysaccharide acid of high molecular weight, which is apparently in the vitreous humor in a salt-like combination. It appears to be a substance unique in higher animals, and may be best compared with some of the specific polysaccharides of bacteria.

EXPERIMENTAL

Our starting material was the acetone precipitate of fresh cattle vitreous humor. Lots of 100 eyes were brought from the abattoir packed in ice; the vitreous humor was immediately removed, strained through loose cotton gauze, and poured into 10 times its volume of cold acetone with vigorous stirring. After standing overnight in the ice box, it was filtered by suction, washed abun-

dantly with acetone and ether, dried *in vacuo* over P_2O_5, and powdered. The yield from 100 eyes was about 3.2 gm., containing about 7 per cent nitrogen, 11 per cent moisture, and 40 per cent ash (ashed with H_2SO_4). The pH of an aqueous suspension of this powder was greater than 10, while the original vitreous humor has a pH of about 7.8. This alkaline reaction cannot be explained by loss of CO_2. The supernatant acetone after evaporation was also alkaline. By a similar treatment, no carbonate was formed from bicarbonate. Other protein solutions, *e.g.* serum, become slightly more acid after acetone precipitation.

In the first experiments aqueous extracts of the acetone powder were precipitated by acidified alcohol. The powders thus obtained had 5 to 6 per cent nitrogen and 30 to 40 per cent reducing substances as glucose (Hagedorn-Jensen method (4) after 2 hours of hydrolysis in sealed tubes with 2 N H_2SO_4 in boiling water). Their solutions were not precipitated by dilute acetic acid, barium hydroxide, or neutral lead acetate, but were precipitated by basic lead acetate. The Molisch reaction was strongly positive. From the analytical figures and the reactions it was evident that the substance was not a mucoid, but a polysaccharide.

For obtaining the purified polysaccharide acid, the acetone powder from 100 eyes is extracted three times with 200 cc. portions of 90 per cent acetic acid. The residue is washed with alcohol until most of the acetic acid is removed, then suspended in water, and neutralized with N NaOH to facilitate centrifuging. This extraction with water is repeated on the centrifuged residue.

This residue consists of a fibrous mass, insoluble in all solvents except hot alkali, having a nitrogen content of 13.5 per cent (ash-free), and giving a strong Molisch reaction after hydrolysis. It is similar to collagen, and probably identical with the "residual protein" of Duke-Elder (2). Its yield is between 0.7 and 1.0 gm. per 100 eyes.

The combined aqueous extracts from above are poured into 6 times their volume of alcohol to which a few cc. of glacial acetic acid are added. After standing cold overnight, the mixture is centrifuged, taken up in a small volume of water, and poured into 15 times the volume of glacial acetic acid. The stringy material stands overnight in the ice box, and is washed abundantly with alcohol, acetone, and ether, powdered, and dried *in vacuo* over

P_2O_5. The yield from 100 eyes is about 0.73 gm.; *i.e.*, 30 per cent of the organic material. It contains a varying amount of inorganic material (2 to 10 per cent), mostly $CaSO_4$, most of which can be removed by dissolving in 0.2 N HCl and reprecipitating in glacial acetic acid.

By a similar procedure no polysaccharide was obtained from egg white.

In Table I are given some of the data on the preparations of this acid for which we propose, for convenience, the name "hyaluronic acid," from hyaloid (vitreous) + uronic acid.

TABLE I

Analysis of Preparations of Hyaluronic Acid

Preparation No.	Per cent nitrogen	Reducing substance as per cent glucose*		Equivalent weight	Per cent ash	Remarks
		(*a*)	(*b*)			
4-A	4.77	49.4	58.9	460†	4.04	
20-A	5.16	49.0	61.2	464	3.48	20.5% hexuronic acid
27-III	4.41	52.6	60.7	446	10.1	
30-I‡	3.84	51.0	59.4	453	1.01	20.5% acetyl

* (*a*) indicates values obtained after precipitation of the neutralized hydrolysate with $Zn(OH)_2$; (*b*) indicates values obtained directly on the neutralized hydrolysate.

† Electrometric titration value 507.

‡ Prepared from Preparation 27-III by reprecipitating from 0.2 N HCl in glacial acetic acid.

The free acid is very hygroscopic, but is not easily soluble in water. The salts are very soluble, forming highly viscous solutions. The following qualitative tests were positive: carbohydrate (Molisch), pentose (Bial), pentose or hexuronic acid (Tollens' phloroglucinol), hexuronic acid (Tollens' naphthoresorcinol), amino sugar (Elson and Morgan (5)); the following were negative: protein (biuret), galactose (mucic acid formation). The preparations contain no phosphorus, and those with a low ash content contain only traces of sulfur (shown to be $CaSO_4$).

Optical rotation in 2 per cent neutral solution in a 0.25 dm. tube, sodium light, was 0°; after hydrolysis, in 1.13 per cent solution, in a 1 dm. tube, −0.07° at 30°, sodium light.

In one preparation (No. 20-A) we found 20.5 per cent uronic acid calculated as hexuronic acid (6) (0.1995 gm. gave 0.01774 gm. of CO_2). As a check on the method, 0.2072 gm. of pure glucuronic acid (for which we wish to thank Mr. L. L. Engel of the Department of Biological Chemistry) gave 0.0480 gm. of CO_2 compared with a theoretical of 0.0470 gm. In Preparation 30-I, acetyl estimations by a slight modification of the method of Kuhn and Roth (7) showed 20.5 per cent acetyl, indicating two acetyl groups per equivalent weight.

The quantitative amino sugar estimation (5) was unreliable, since the color from the glucosamine hydrochloride standard (violet-red) did not match well with the color produced by the hydrolysate (brown-red). With different standards we obtained values between 46 and 64 per cent of total nitrogen as amino sugar nitrogen, or 35 to 49 per cent of the total reducing substance as hexosamine.

The reducing sugar content before hydrolysis indicated one reducing group present for about fourteen after hydrolysis. The hydrolysate yielded a mixture of phenylosazones which we have not as yet been able to separate.

On electrotitration with the glass electrode in a current of hydrogen to exclude CO_2 we obtained an apparent equivalent weight of 507 (18.56 mg. required 3.31 cc. of 0.01106 N NaOH), while the value by titration, with phenolphthalein as the indicator, was between 446 and 464. The electrotitration was made in a volume of about 80 cc., while the final volume in the colorimetric titration was about 4 cc. With the electrotitration data the apparent dissociation constant, calculated from the formula of Van Slyke (8), is 4.58×10^{-5} at 32°, and the acid is therefore about 2.5 times stronger than acetic acid. (We wish to thank Mr. F. Rosebury of the Department of Biological Chemistry for assistance with the electrotitration.)

It is evident that hyaluronic acid is not identical with what Levene and López-Suárez (9) considered a mucoitin sulfuric acid prepared from vitreous humor by alkaline treatment. Their material contained 3.6 per cent sulfur, while our material contains only traces as an impurity ($CaSO_4$).

One might suspect that the "mucoid" obtained by acidification of the fresh vitreous humor should be in our insoluble residue,

since the latter gives a strong Molisch reaction after hydrolysis. However, the known mucoids retain their solubility in water after treatment with acetone or similar agents.

When the 90 per cent acetic acid extract above is evaporated, the residue taken up in water, and made alkaline with ammonium or sodium hydroxide, a precipitate is obtained containing on an ash-free basis 17.1 per cent nitrogen. The yield from 100 eyes is about 0.25 gm. The material is soluble in dilute acids and is reprecipitated by alkalies. On dialysis in 0.1 N HCl it passes through the collodion membrane. It seems to be of the nature of a histone or a simpler base.

It is noteworthy that, according to Redslob (10), Abé found in vitreous humor two isoelectric points, one at pH 3.8, the other at pH 9.4. The latter would probably correspond to a complex containing the above basic substance.

One may speculate as to the possible connection between the polysaccharide acid and the problem of glaucoma. Redslob and Reiss (11) have demonstrated that the injection of alkali into the vitreous humor produces a long lasting rise in intraocular pressure, while the introduction of acid or neutral solutions causes only transient changes. They also state that the introduction of acid into a glaucomatous eye lowered the tension and relieved the symptoms. They report the production in the rabbit of a picture "with all clinical symptoms of glaucoma" by isotonic sodium hydroxide injection. There is a possibility of the spontaneous occurrence of such an alkaline reaction by the lactonization of the polysaccharide acid and the simultaneous liberation of the base which originally neutralized it.

SUMMARY

From the vitreous humor of cattle eyes a polysaccharide acid of high molecular weight has been obtained by methods avoiding strong hydrolytic agents. The acid has an apparent equivalent weight of about 450. As constituents there have been recognized a uronic acid, an amino sugar, and possibly a pentose. The dissociation constant has been determined as 4.58×10^{-5} at 32°. An attempt will be made to relate the acid to the pathogenesis of glaucoma.

The authors wish to thank Dr. John M. Wheeler for his encouragement and interest in this work.

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Application Number	09/879,959
Filing Date	06/13/2001
First Named Inventor	Paul H. Weigel, et al.
Group Art Unit	1653
Examiner Name	~~G. Bugaisky~~ R. Utz
Attorney Docket Number	35541.049

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	1	~~4168888~~		~~Hartman et al.~~	~~10/02/1979~~	
MW	2	4224179		Schneider	09/23/1980	
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MW	4	4511478		Nowinski, et al.	04/16/1985	
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MW	H		95/24497 WO		Lansing, et al.	09/14/1995		
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	24	~~5616244~~		~~Lee, et al.~~	~~03/11/1997~~	
	25	~~5622850~~		~~Sierra, et al.~~	~~04/22/1997~~	
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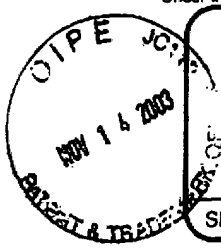

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Examiner Name	~~C. Bugaisky~~ L. Ulm
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	WW	"MOLECULAR CLONING, IDENTIFICATION, AND SEQUENCE OF THE HYALURONAN SYNTHASE GENE FROM GROUP A STREPTOCOCCUS PYOGENES," DeAngelis, et al., J. Biol. Chem., Vol. 268, No. 26, pp. 19181-19184, (1993).	
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Summary

The United States Patent and Trademark Office (Office or USPTO) plans in the near future to: (1) cease mailing copies of U.S. patents and U.S. patent application publications (US patent references) with Office actions except for citations made during the international stage of an international application under the Patent Cooperation Treaty and those made during reexamination proceedings; and (2) provide electronic access to, with convenient downloading capability of, the US patent references cited in an Office action via the Office's private Patent Application Information Retrieval (PAIR) system which has a new feature called "E-Patent Reference." Before ceasing to provide copies of U.S. patent references with Office actions, the Office shall test the feasibility of the E-Patent Reference feature by conducting a two-month pilot project starting with Office actions mailed after December 1, 2003. The Office shall evaluate the pilot project and publish the results in a notice which will be posted on the Office's web site (www.USPTO.gov) and in the Patent Official Gazette (O.G.). In order to use the new E-Patent Reference feature during the pilot period, or when the Office ceases to send copies of U.S. patent references with Office actions, the applicant must: (1) obtain a digital certificate from the Office; (2) obtain a customer number from the Office, and (3) properly associate applications with the customer number. The pilot project does not involve or affect the current Office practice of supplying paper copies of foreign patent documents and non-patent literature with Office actions. Paper copies of references will continue to be provided by the USPTO for searches and written opinions prepared by the USPTO for international applications during the international stage and for reexamination proceedings.

Description of Pilot Project to Provide Electronic Access to Cited U.S. Patent References

On December 1, 2003, the Office will make available a new feature, E-Patent Reference, in the Office's private PAIR system, to allow more convenient downloading of U.S. patents and U.S. patent application publications. The new feature will allow an authorized user of private PAIR to download some or all of the U.S. patents and U.S. patent application publications cited by an examiner on form PTO-892 in Office actions, as well as U.S. patents and U.S. patent application publications submitted by applicants on form PTO/SB08 (1449) as part of an IDS. The retrieval of some or all of the documents may be performed in one downloading step with the documents encoded as Adobe Portable Document format (.pdf) files, which is an improvement over the current page-by-page retrieval capability from other USPTO systems.

USPTO TO PROVIDE ELECTRONIC ACCESS TO CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS AND CEASE SUPPLYING PAPER COPIES

In support of its 21st Century Strategic Plan goal of increased patent e-Government, beginning in June 2004, the United States Patent and Trademark Office (Office or USPTO) will begin the phase-in of its E-Patent Reference program and hence will: (1) **provide downloading capability of the U.S. patents and U.S. patent application publications cited in Office actions** via the E-Patent Reference feature of the Office's Patent Application Information Retrieval (PAIR) system; and (2) **cease mailing paper copies of U.S. patents and U.S. patent application publications with Office actions** (in applications and during reexamination proceedings) except for citations made during the international stage of an international application under the Patent Cooperation Treaty (PCT). In order to use the new E-Patent Reference feature applicants must: (1) obtain a digital certificate and software from the Office; (2) obtain a customer number from the Office; and (3) properly associate patent applications with the customer number. Alternatively, copies of all U.S. patents and patent application publications can be accessed without a digital certificate from the USPTO web site, from the USPTO Office of Public Records, and from commercial sources. The Office will continue the practice of supplying paper copies of foreign patent documents and non-patent literature with Office actions. Paper copies of cited references will continue to be provided by the USPTO for international applications during the international stage.

Schedule

June 2004	TCs 1600, 1700, 2800 and 2900
July 2004	TCs 3600 and 3700
August 2004	TCs 2100 and 2600

All U.S. patents and U.S. patent application publications are available on the USPTO web site. However, a simple system for downloading the cited U.S. patents and patent application publications has been established for applicants, called the E-Patent Reference system. As E-Patent Reference and Private PAIR require participating applicants to have a customer number, retrieval software and a digital certificate, all applicants are strongly encouraged to contact the Patent Electronic Business Center to acquire these items. To be ready to use this system by June 1, 2004, contact the Patent EBC as soon as possible by phone at 866-217-9197 (toll-free), 703-305-3028 or 703-308-6845 or electronically via the Internet at ebc@uspto.gov.

Other Options

The E-Patent Reference function requires the applicant to use the secure Private PAIR system, which establishes confidential communications with the applicant. Applicants using this facility must receive a digital certificate, as described above. Other options for obtaining patents which do not require the digital certificate include the USPTO's free Patents on the Web program (http://www.uspto.gov/patft/index.html). The USPTO's Office of Public Records also supplies copies of patents for a fee (http://ebiz1.uspto.gov/oems25p/index.html). Commercial sources also provide U.S. patents and patent application publications.

For complete instructions see the Official Gazette Notice, USPTO TO PROVIDE ELECTRONIC ACCESS TO CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS AND CEASE SUPPLYING PAPER COPIES, on the USPTO web site.

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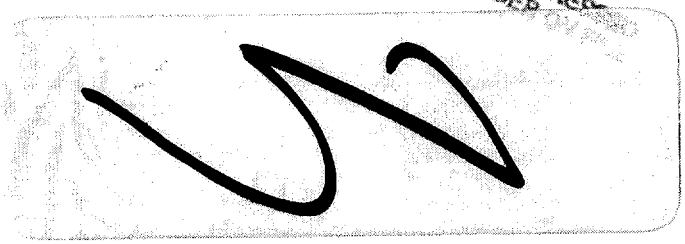

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